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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,232	04/12/2001	Philip Leder	00383/052002	6202

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 06/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,232	LEDER ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The substitute specification filed January 15, 2002 has not been entered because it does not conform to 37 CFR 1.125(b) because: the specification may contain new matter.

The substitute specification has added Figure 12D which was not part of the originally filed application. The original specification stated two EST clones were assigned GenBank Accession Numbers, including AF218941. These Genbank Accession Numbers were not incorporated by reference. Moreover, Genbank Accession Numbers are subject to updates and changes such that they may not have been identical to the instantly filed SEQ ID NO: 5.

While it is noted that the provisional application, which has been incorporated by reference, provides a sequence which appears to closely resemble newly added SEQ ID NO: 5. However, since the provisional application does not contain a sequence listing, a comparison of the two sequences is not possible. Moreover, the Genbank identifiers of the two sequences, while similar, do differ, namely AF213942 and AF218942. Clarification is requested.

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, pages 10 and 37 contain hyperlinks.

Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

The specification contains numerous sequences which do not contain SEQ ID NO: identifiers. It is noted that the changes made to the substitute specification would address this objection, but the substitute specification has not been entered.

Priority

4. This application claims priority to provisional application 60/196,811, filed April 13, 2001.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6 are drawn to determining whether a patient has an increased risk for recurrent pregnancy loss by detecting mutations, polymorphisms, expression levels, and biological activity of forming-2.

The specification has also analyzed the expression patterns of Fmn-2 in adult mouse brain. The specification describes generating a Fmn-2 deficient mouse (page 13). The specification states that Fmn-2 -/- mice were analyzed and breed with male mice such that the deciduas was analyzed. The deciduas from the Fmn-2 -/- females exhibited significant differences in embryonic developments, such as no visible embryonic tissue, embryos at various stages of developmental arrest and normal embryo (page 14). Moreover, the specification teaches that "in the mouse, when part of this gene is deleted, 97-100% of oocytes are unable to complete meiosis correctly" (page 17, lines 4-8). Moreover, "since the molecular role of Fmn-2 appears to have been conserved in yeast, fruit flies, and mice, it is likely that Fmn-2 will function similarly in humans. Thus, one can identify the cause of recurrent pregnancy loss by detecting mutations in Fmn-2" (page 17, lines 8-10). The specification also speculates that "mutations in Fmn-2 that decrease Fmn-2 biological activity may be correlated with recurrent pregnancy loss in humans" (page 18, lines 4-6). Similarly, "a decrease or increase in the level of Fmn-2 production may provide an indication of a deleterious condition" (page 18, lines 6-7). With respect to protein levels, "these levels would be compared to wild-type Fmn-2 levels" (page 19, lines 5-6). The specification performed a northern blot and RNA dot blot using the entire 3' human EST (page 24, lines 24-28). The specification teaches that two human BACS containing Fmn-2 genomic sequence

were sequenced. These sequence will "at a later date, these pieces will be correctly ordered and the nucleotide numbering will be consistent throughout the BAC" (pages 37).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has not defined any naturally occurring polymorphisms within a Fmn-2 nucleic acid sequence which are associated with

recurrent pregnancy loss, nor any analysis of Fmn-2 expression levels in affected individuals.

First, it is unclear what is encompassed by a formin2 gene (Fmn-2). The specification teaches a mouse amino acid sequence SEQ ID NO: 2 and the corresponding cDNA sequence. This is not description of a gene since a gene encompasses promoter regions, upstream, downstream and intronic regions. Moreover, the specification's teachings of two Fmn-2 EST sequences is not description of a Fmn-2 gene. Moreover, it is unclear which sequence is the "normal" Fmn-2 sequence and which is the variant. The two human BACs containing Fmn-2 (SEQ ID NO: 6-7) do not indicate the essential features of the Fmn-2 gene such that the skilled artisan would recognize that the specification had described a Fmn-2 gene.

Second, the specification fails to teach any naturally occurring mutations within a Fmn-2 nucleic acid. While the specification analyzes mice which lack Fmn-2 gene, the specification has not described any naturally occurring mutations within Fmn-2. The broad genus of mutations and polymorphisms encompasses, but is not limited to, point mutations, tranlocations, inversions, insertions, deletions. The specification has not described any such mutations and/or polymorphisms within the Fmn-2 gene.

Third, the specification has not provided any analysis of Fmn-2 biological activity nor expression levels in affected and unaffected patients. The specification has not described normal nor abnormal levels of Fmn-2 levels for either RNA or polypeptides such that the artisan would recognize that the applicant was in possession of the claimed invention at the time the application was filed. While Northerns have been

done, there is no description of how to identify a decreased level of Fmn-2 as compared to normal. The specification has not provided any threshold for determining significant variation between expression levels within abnormal and normal individuals.

Fourth, the specification has not provide any correlation between a Fmn-2 nucleic acid an recurrent pregnancy loss. The specification has not provided any sample of affected individuals with a specific polymorphism within Fmn-2 nucleic acids as compared to nonaffected individuals. Since the specification lacks teachings of mutations, polymorphisms and decreased levels, the analysis of how these elements affect recurrent pregnancy loss has not been analyzed.

Therefore, the specification does not appear to have described mutations, polymorphisms, decreased levels of expression or biological activity and their association with recurrent pregnancy loss. The specification has not clearly provided that the presence of mutations is indicative of increased risk as opposed to protective mutations which would be indicative of decreased risk. The specification does not clearly provide whether increased or decreased levels of Fmn-2 are associated with recurrent pregnancy loss as evidenced by "a decrease or increase in the level of Fmn-2 production may provide an indication of a deleterious condition" (page 18, lines 6-7). Therefore, at the time the invention was made applicant does not appear to be in possession of the claimed invention.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-6 are drawn to broadly drawn to determining whether a patient has an increased risk for recurrent pregnancy loss by detecting mutations, polymorphisms, expression levels, and biological activity of forming-2.

The specification has also analyzed the expression patterns of Fmn-2 in adult mouse brain. The specification describes generating a Fmn-2 deficient mouse (page 13). The specification states that Fmn-2 -/- mice were analyzed and breed with male mice such that the deciduas was analyzed. The deciduas from the Fmn-2 -/- females exhibited significant differences in embryonic developments, such as no visible embryonic tissue, embryos at various stages of developmental arrest and normal embryo (page 14). Moreover, the specification teaches that "in the mouse, when part of this gene is deleted, 97-100% of oocytes are unable to complete meiosis correctly" (page 17, lines 4-8). Moreover, "since the molecular role of Fmn-2 appears to have been conserved in yeast, fruit flies, and mice, it is likely that Fmn-2 will function similarly in humans. Thus, one can identify the cause of recurrent pregnancy loss by detecting mutations in Fmn-2" (page 17, lines 8-10). The specification also speculates that

"mutations in Fmn-2 that decrease Fmn-2 biological activity may be correlated with recurrent pregnancy loss in humans" (page 18, lines 4-6). Similarly, "a decrease or increase in the level of Fmn-2 production may provide an indication of a deleterious condition" (page 18, lines 6-7). With respect to protein levels, "these levels would be compared to wild-type Fmn-2 levels" (page 19, lines 5-6). The specification performed a northern blot and RNA dot blot using the entire 3' human EST (page 24, lines 24-28). The specification teaches that two human BACS containing Fmn-2 genomic sequence were sequenced. These sequence will "at a later date, these pieces will be correctly ordered and the nucleotide numbering will be consistent throughout the BAC" (pages 37).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, it is unclear what is encompassed by a formin2 gene (Fmn-2). The specification teaches a mouse amino acid sequence SEQ ID NO: 2 and the corresponding cDNA sequence. This is not description of a gene since a gene encompasses promoter regions, upstream, downstream and intronic regions. Moreover, the specification's teachings of two Fmn-2 EST sequences is not description of a Fmn-2 gene. Moreover, it is unclear which sequence is the "normal" Fmn-2 sequence and which is the variant. The two human BACs containing Fmn-2 (SEQ ID NO: 6-7). The skilled artisan would be required to perform undue experimentation to determine the full structure of the Fmn-2 gene as required by the claims. Moreover, the skilled artisan would be required to determine what a human Fmn-2 gene encompassed and how to identify a gene as a Fmn-2 gene.

Second, the specification fails to teach any naturally occurring mutations within a Fmn-2 nucleic acid. While the specification analyzes mice which lack Fmn-2 gene, the specification has not described any naturally occurring mutations within Fmn-2. The broad genus of mutations and polymorphisms encompasses, but is not limited to, point mutations, tranlocations, inversions, insertions, deletions. The specification has not taught any such mutations and/or polymorphisms within the Fmn-2 gene. Determining and locating mutations within an undisclosed gene would require undue and unpredictable experimentation. The skilled artisan would first be required to determine what nucleic acid sequences are normal and then determine variations or mutations of the sequence.

Third, the specification has not provided any analysis of Fmn-2 biological activity nor expression levels in affected and unaffected patients. The specification has not described normal nor abnormal levels of Fmn-2 levels for either RNA or polypeptides such that the artisan would recognize that the applicant was in possession of the claimed invention at the time the application was filed. While Northerns have been done, there is no description of how to identify a decreased level of Fmn-2 as compared to normal. The specification has not provided any threshold for determining significant variation between expression levels within abnormal and normal individuals. It would require undue experimentation for the skilled artisan to determine the limitations of a decreased level of Fmn-2 expression and biological activity.

Fourth, the specification has not provide any correlation between a Fmn-2 nucleic acid an recurrent pregnancy loss. The specification has defined a "increased

risk [for] recurrent pregnancy loss" as "the likelihood for two or more spontaneous abortions is at least twice as high as it is for an average women of the same age and ethnicity". The specification has not provided any sample of affected individuals with a specific polymorphism within Fmn-2 nucleic acids as compared to nonaffected individuals. Since the specification lacks teachings of mutations, polymorphisms and decreased levels, the analysis of how these elements affect recurrent pregnancy loss has not been analyzed. The skilled artisan in addition to determining mutations and polymorphisms within the undisclosed gene, would be required to analyze the variations to determine whether the mutations or polymorphisms were correlated in any respect to recurrent pregnancy loss. It is noted that Claim 6 is directed to "altered risk", but the skilled artisan would be further required to determine whether the altered risk was increased or decreased or altered in another way. It is unpredictable that such a mutation exists within the gene and further unpredictable without undue experimentation that a discovered mutation is associated with an increase of such a condition. Moreover, it is unpredictable whether an increase in expression or a decrease in expression of Fmn-2 is associated with recurrent pregnancy loss because the specification is silent with respect to such a teaching. Prior to using the claimed method, the skilled artisan would be required to isolate a Fmn-2 gene, identify a polymorphism within a certain age group and ethnicity and determine whether the polymorphism is associated with increased recurrent pregnancy loss. There is no reasonable expectation of success that any one mutation is associated with recurrent

pregnancy loss or whether increased/decreased expression affects the disorder. Trial and error experimentation to practice the claimed invention would be required.

Therefore, the specification does not appear to have enabled the skilled artisan to analyzed mutations, polymorphisms, decreased levels of expression or biological activity and their association with recurrent pregnancy loss. The specification has not clearly provided that the presence of mutations is indicative of increased risk as opposed to protective mutations which would be indicative of decreased risk. The specification does not clearly provide whether increased or decreased levels of Fmn-2 are associated with recurrent pregnancy loss as evidenced by "a decrease or increase in the level of Fmn-2 production may provide an indication of a deleterious condition" (page 18, lines 6-7). Therefore, at the time the invention was made applicant does not appear to have enabled the skilled artisan how to make and used the claimed invention.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg J. Goldberg
May 28, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600